Blisters 101

Autoimmune Bullous Diseases for the non-Dermatologist

April 2, 2014

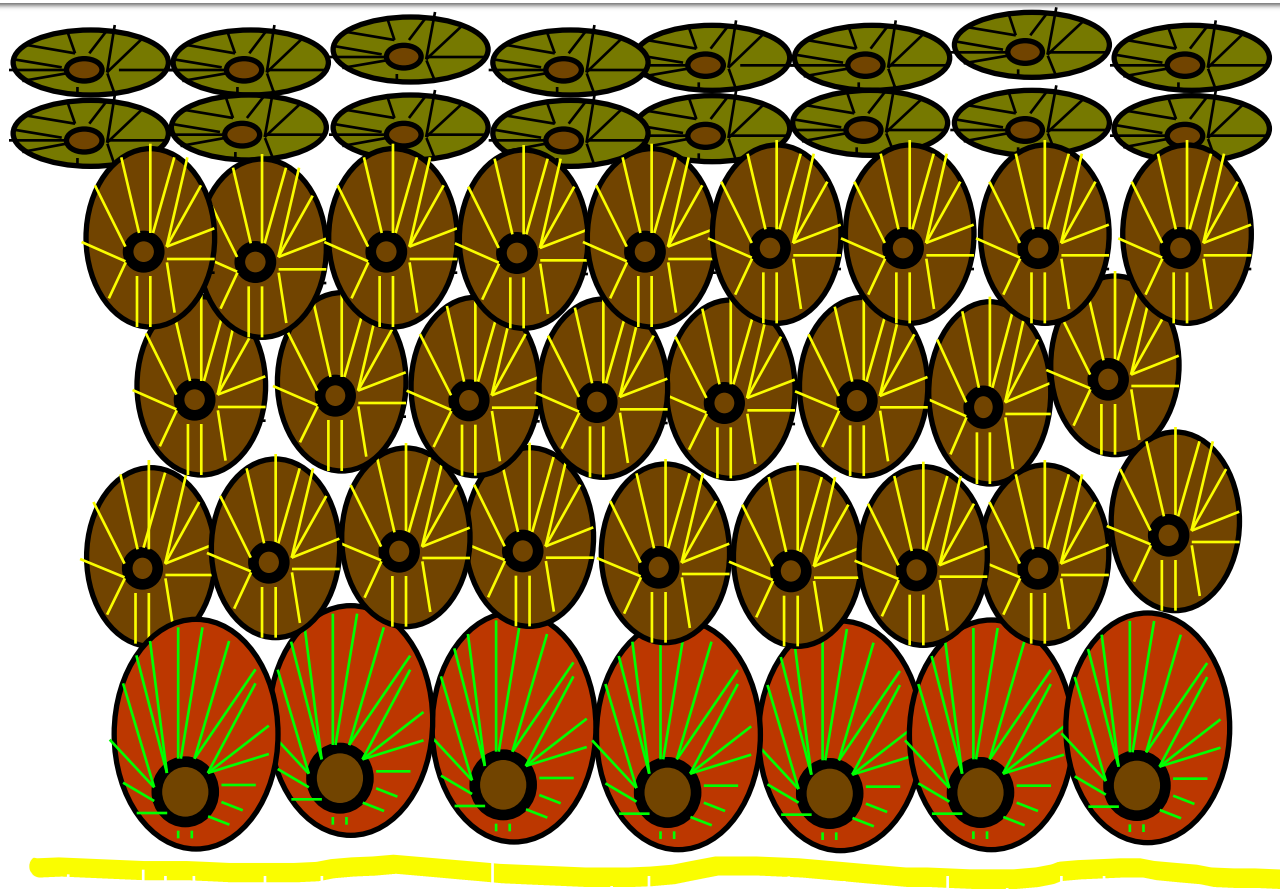
Conflicts of Interest

- None
- Will discuss off-label uses

Causes of Cutaneous Blistering

- Traumatic
- Infectious
- Genetic
- Allergic (contact dermatitis, drug)
- Autoimmune

Structure of the Epidermis



Cornified Layer

Subcorneal Layer

Suprabasal Layer

Basal Layer

MSL / 1998

PEMPHIGUS GROUP – Cell-Cell Adhesion

Pemphigus vulgaris – Desmoglein 1, 3
Pemphigus foliaceus – Desmoglein 1
Paraneoplastic pemphigus – Desmoglein 3, Plakin family members

PEMPHIGOID GROUP – Cell Substrate Adhesion

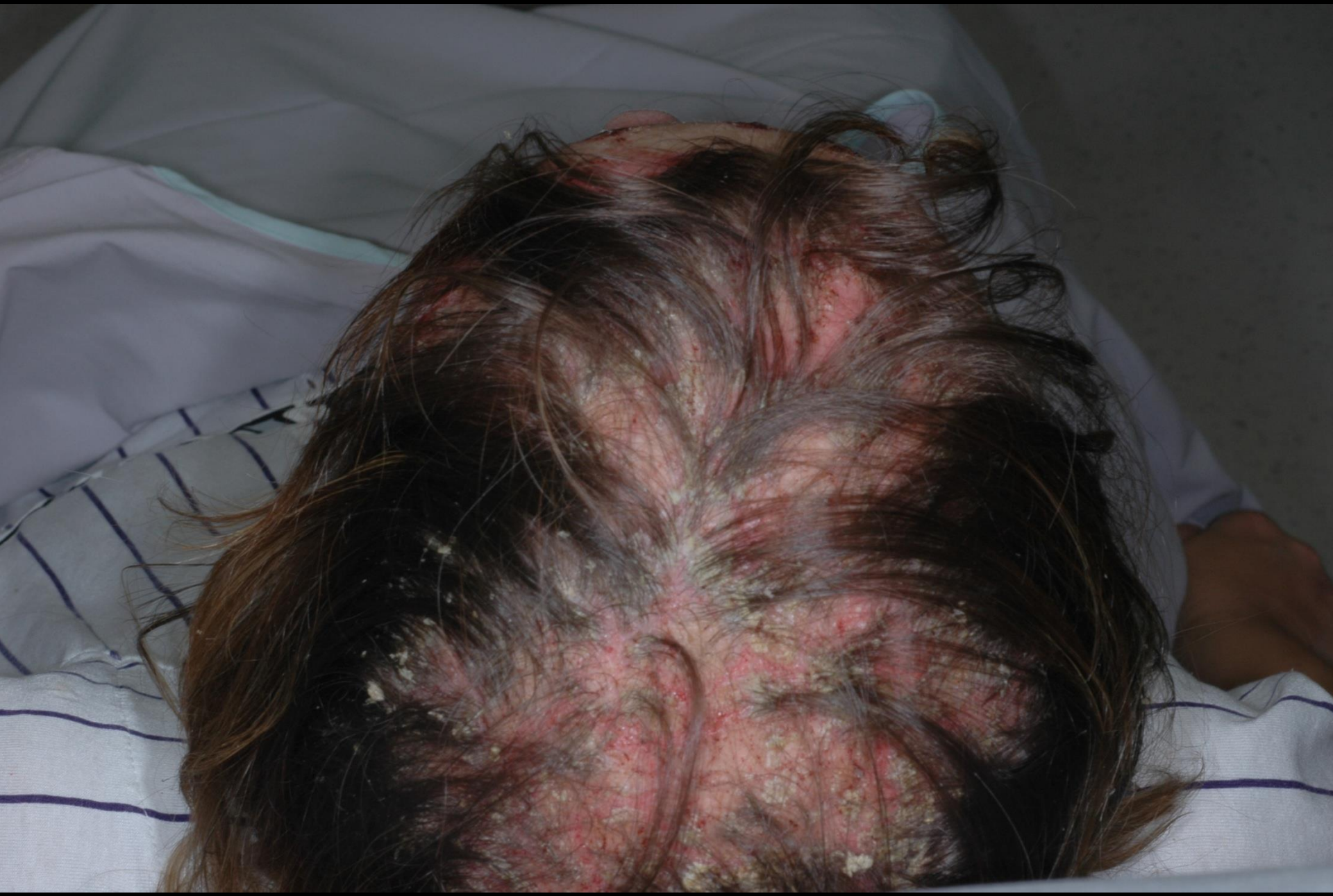
Bullous pemphigoid – BP180, BP240
Pemphigoid gestationis – BP180
Linear IgA Disease – 120 kD processed form of BP180
Cicatricial pemphigoid – BP180, Laminin 3,3,2, col VII

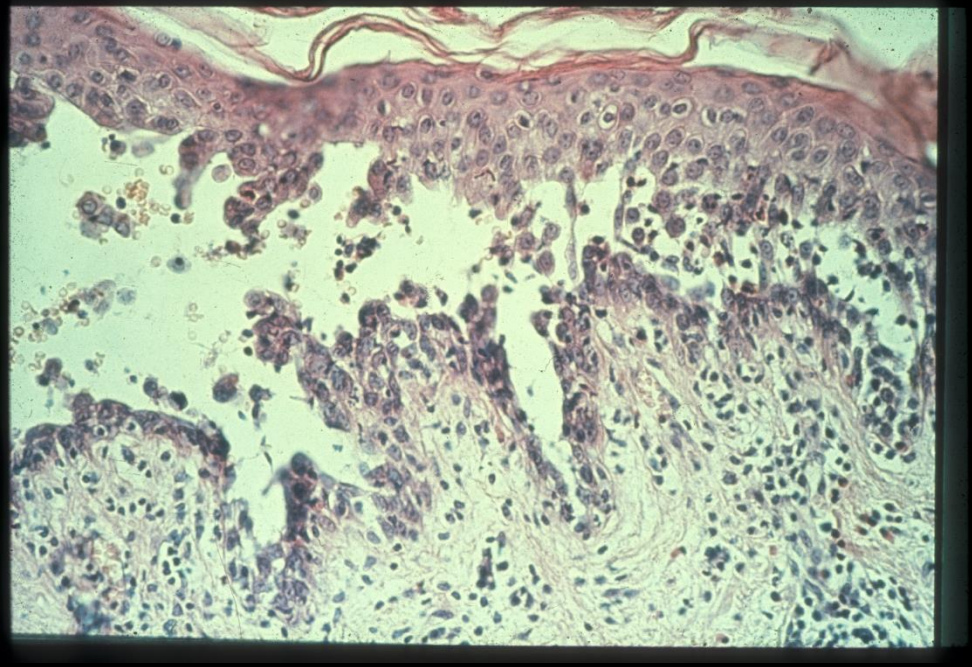
MISCELLANEOUS

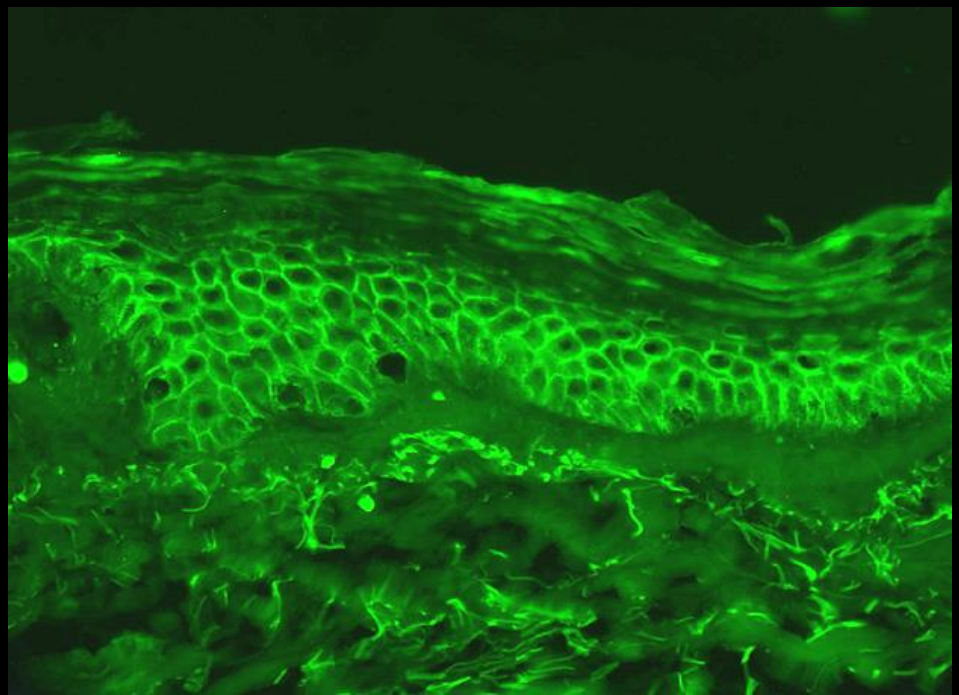
Dermatitis herpetiformis - e-Transglutaminase
Epidermolysis bullosa acquisita – Coll VII
Bullous SLE – Coll VII

History

- 41 year old female
- August 2007: Developed "bumps" on her scalp - diagnosed as psoriasis, then tinea
- October 2007 – Spread to chest and trunk – diagnosed as bullous pemphigoid
- November 2007 – seen at UIHC, biopsy and immunofluorescent studies performed





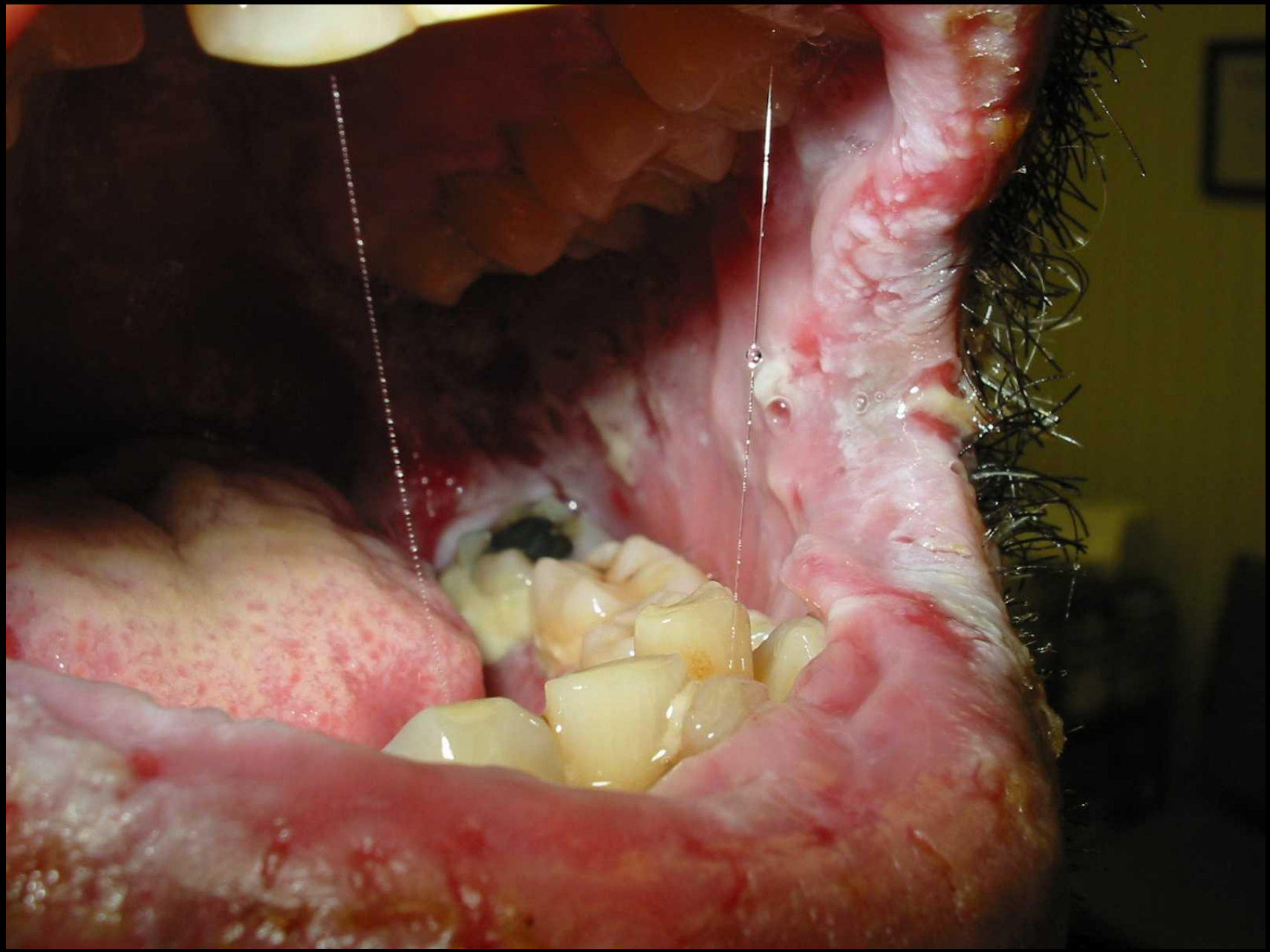


Diagnosis of PV

- Clinical
- H&E Biopsy
- Direct Immunofluorescence
- Indirect Immunofluorescence
- ELISAs (not for initial screening)

PEMPHIGUS VULGARIS

- 70% begin in the mouth. Scalp is the next most common spot. Left untreated widespread involvement will develop.
- Flaccid blisters that arise on normal appearing skin.
- Significant mucous membrane involvement

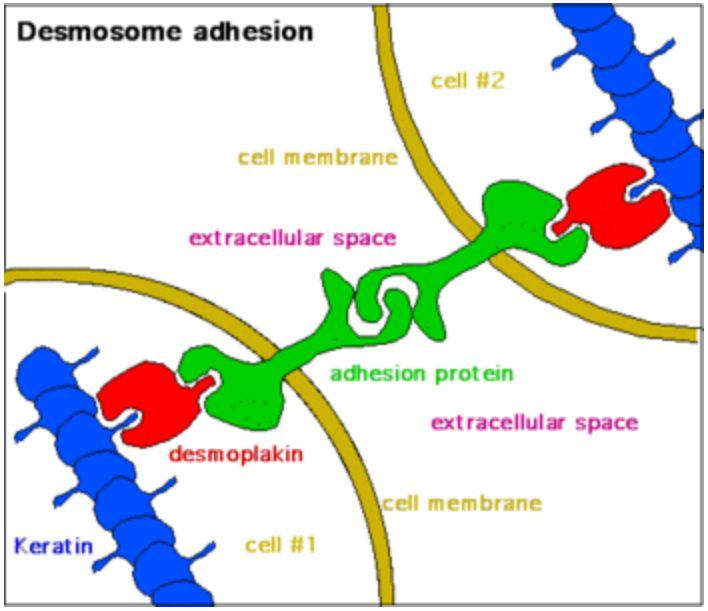


PEMPHIGUS VULGARIS

- Average onset 5th decade
- M=F, more common in Ashkenazi Jewish population
- Generally a life-long disease
- Pre-steroid era the fatality rate approached 100% at 5 years
- Currently: 5-20% at 5 years (mainly due to side effects of therapy)

PEMPHIGUS GROUP

- Autoantibodies directed against desmosomal cadherins – calcium dependent cell adhesion molecules
- PV – Desmoglein 3
- PF – Desmoglein 1

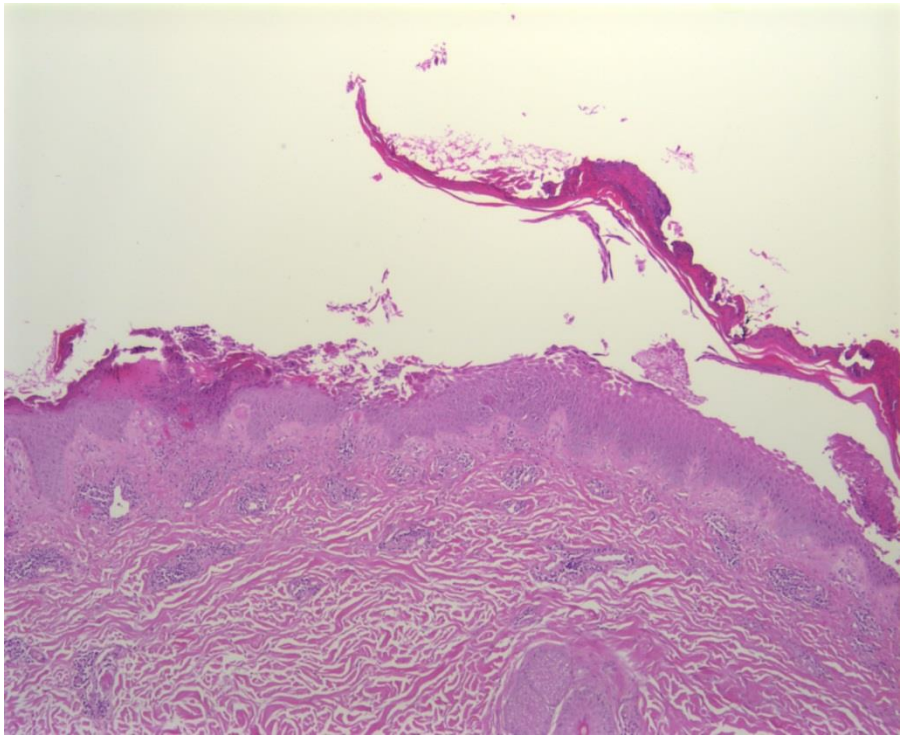


Pemphigus variants

- Pemphigus foliaceus
- Paraneoplastic pemphigus
- Drug induced

PEMPHIGUS FOLIACEUS

- Blisters at level of the stratum corneum
- Flaccid bullae and crusts, predominantly in sun-exposed areas
- No mucosal involvement
- Tends to respond more easily to treatment than PV



Paraneoplastic pemphigus

- Significant mucous membrane involvement (often ocular
- Cutaneous involvement highly variable
- Non-Hodgkins lymphoma, Castleman's tumor

Drug Induced Pemphigus

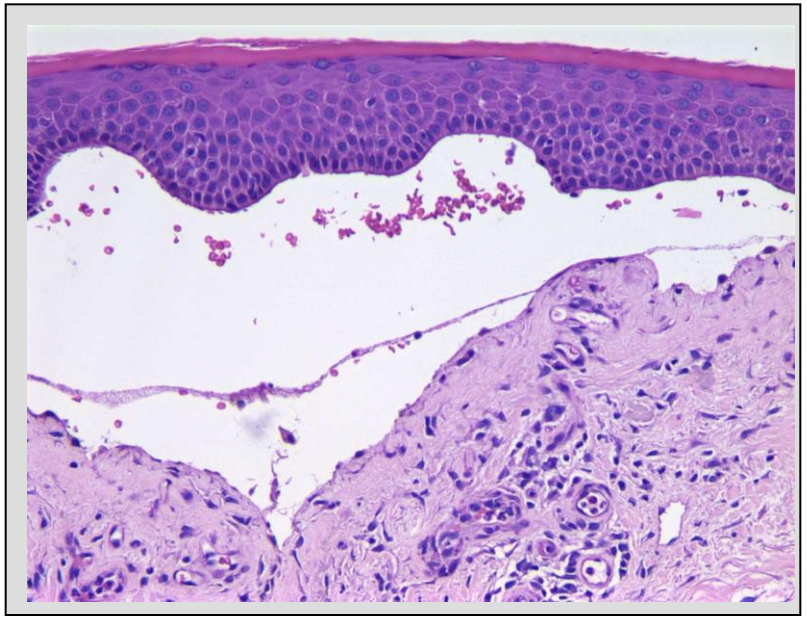
- PF > PV (4:1)
- Thiol or sulfur containing drugs: penicillamine, captropril, enalapril, penicillin, cephalosporins, piroxicam
- Most resolve when the medication is withdrawn

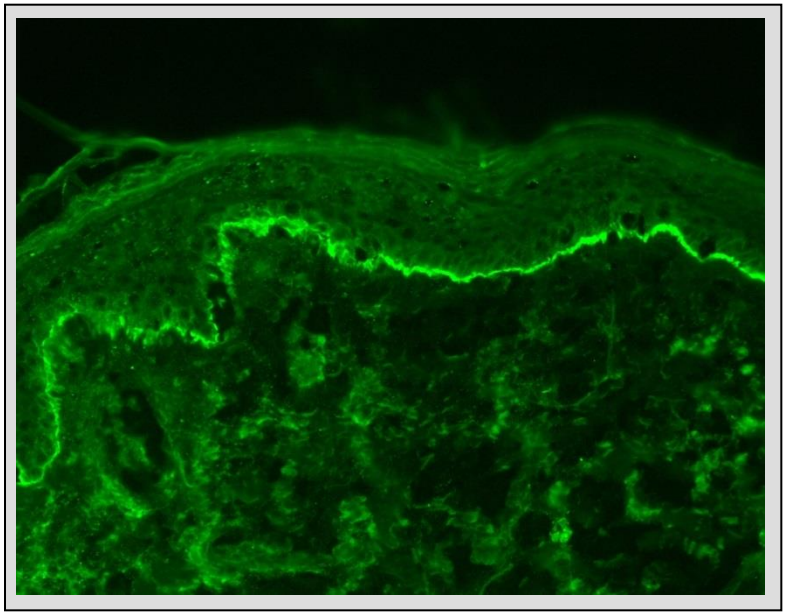
PEMPHIGOID GROUP

HISTORY

- A 82 year-old woman is transported from a nursing home for a two week history of a rash with blisters developing in the past week
- Medical history: diabetic, hypertensive, Parkinson's disease

BULLOUS PEMPHIGOID





BULLOUS PEMPHIGOID

- M=F, Average age 76
- IgG and IgE class autoantibodies target BP180 (collagen XVII) – a cell-substrate adhesion molecule of the hemidesmosome
- May be associated with other autoimmune disorders (thyroid, MS)
- Risk factors dementia, Parkinson's disease
- Average duration: 6 years

Pemphigoid variants

- Pemphigoid gestationis
- Linear IgA disease
- Cicatricial pemphigoid

Pemphigoid Gestationis

- Bullous pemphigoid like eruption
- 1:10,000 pregnancies
- Begins in 2-3rd trimester, resolves post-partum
- Begins around umbilicus in 50%
- Papules, urticarial plaques, vesicles and bullae

Linear IgA

- "Cluster of Jewels"
- IgA autoantibodies against processed form of BP180
- Drug induced – vancomycin – resolves with withdrawal of the drug
- Spontaneous
- Juvenile (CBDC)

Cicatricial Pemphigoid

- BP180 (collagen XVII)
- Laminin 3,3,2 (epiligrin)**
- β4 subunit of α6β4 integrin
- Collagen VII

Cancer Risk in AECP

- 35 patients - 10 cancers
- 14 month +/- onset of blistering
- Relative risk 7.7
- Lung, colon, gastric, endometrial

Bullous Diabeticorum

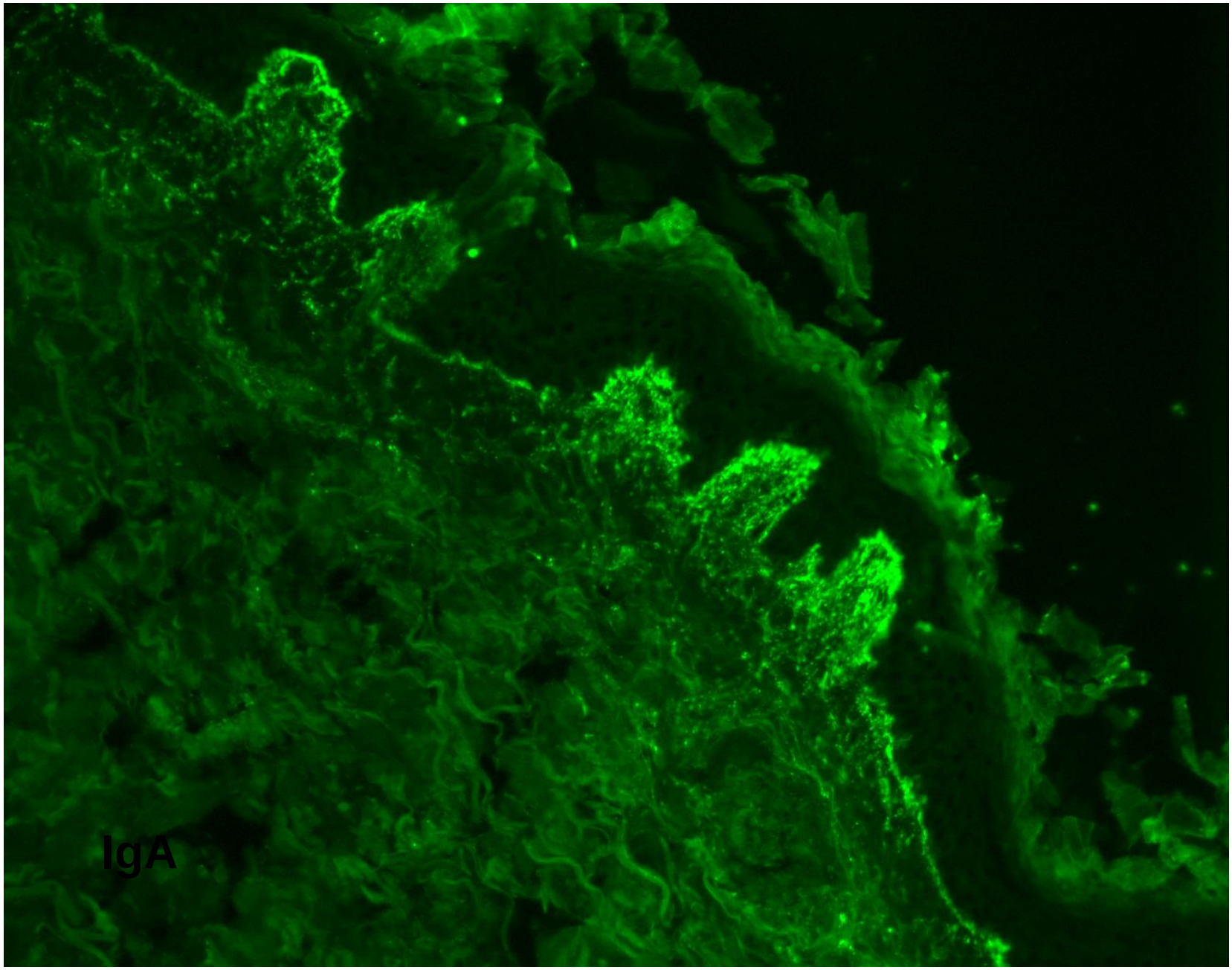
- Acral
- Non-inflammatory
- M > F
- 0.5% of diabetic patients
- Heal spontaneously in 2-6 weeks

History

- 34 year old man with a 2 month history of an extremely pruritic eruption on the knees, elbows and sacrum
- Has been treated for scabies with no response
- Topical steroids do not help

Dermatitis Herpetiformis

- Grouped, **pruritic** vesicles on the extensor elbows, knees and sacrum
- 2^{nd}-4^{th} decade, M>F
- N. European ancestry
- HLA-A1, HLA-B8, HLA-DR3, HLA-DWQ2


IgA

DH & GLUTEN SENSITIVE ENTEROPATHY

- 90% of DH patients have GSE on biopsy
- Most are clinically silent
- 15-20% of celiac disease patients will develop DH
- IgA anti-tissue transglutaminase will be positive in most DH patients
- Increased risk of lymphoma (rr 1.7)

Dermatitis Herpetiformis

- Genetic predisposition to gluten sensitivity
- IgA antibodies to transglutaminase
- Antibody-antigen complex deposits in skin
- IgA antibodies cause PMN chemotaxis and attachment
- PMN release proteolytic enzymes that disrupt the BMZ

DH Treatment

- Gluten free diet (months)
- Dapsone (days)
- Sulfapyridine
- Heparin (recalcitrant cases only)

Minimal response to steroids

Therapy of AIBD

Therapy

- EBM lacking
- Immunosuppressives
  - Prednisone
  - Steroid sparing agents: azathioprine, cytoxan, methotrexate, mycophenolate mofetil
  - Other agents: dapsone, minocycline, colchicine
- Biologics
  - Rituximab
  - Infliximab
- Misc: plasmapheresis, IVIG

Phases of treatment

- **Baseline/Initiation**
- **Consolidation**
  - No new lesions
  - Established lesions starting to heal
- **End of consolidation** (tapering)
  - No new lesions or pruritus (BP) for 2 weeks
  - Majority (~80%) of established lesions healed

Baseline

- Treat!
- Prednisone
  - Up to 0.75 mg/kg/d (BP)
  - Up to 1.5-2 mg/kg/d (PV)
  - 3 weeks
  - Half lives IgG 7-23 d; IgA 4-5d; IgE 2 d
- Clobetasol 40 g/d (European)
- Plasmapheresis
- Immunoadsorption (not available in US currently)
  - Anti-human IgG
  - Protein A

PPD, Ca++, Vit D, bisphosphonates?

Consolidation

- If cannot get prednisone < 10 mg/d consider adjuvant
- Azathioprine
  - TPMT; low and super-high are problematic
  - 2 mg/kg/d
- Mycophenolate mofetil
  - 2-3 gm/d – start low and work up
  - Enteric coated is available
- Methotrexate
  - Weekly doses similar to psoriatic doses – up to 15 mg/week if > 60 kg and no major renal dx
- Cyclophosphamide 

Dapsone

- Love it for DH
- CP –best if IgA mediated
- PV – underpowered studies (IgE pemphigus, pemphigus herpetiformis?)
- EBA – works just about as well as everything else (ie )
- BP – no data

Rule of thumb: IgA or neuts

Rituximab

- Chimeric monoclonal antibody
- Targets CD-20 positive B lymphocytes – removes these cells that are ready to transform into autoantibody producing short-lived plasma cells
- Does not bind to stem cells or plasma cells
- Approved for use in non-Hodgkins lymphomas, rheumatoid arthritis
- Case reports/series of successful treatment of PV, PF, PNP, EBA, CP and BP (more than 100 citations)

Rituximab in Bullous Disease

- Dose: 325 mg/m^2/week x 4 weeks
- Alternative: 1000 mg/week x 2, 2 weeks apart
- Variability in how it is given after the first cycle – repeat in 6 months vs wait for flare
- Monotherapy?

Two months after completing one cycle of rituximab

Adverse Events
Autoimmune Skin Disease (n>2000 pts)

- Serious adverse events – 5-6% (if minimize other immunosuppressants)
- Most commonly infections (sepsis, pneumonia)
- Other reports: prolonged hypo-gammaglobulinemia, neutropenia, DVT, pulmonary embolism
- Progressive multifocal leukoencephalopathy (activation of JC virus – polyoma virus)

THE END